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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,146	09/16/2002	Wilhelm Amberg	51748	9829

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,146	AMBERG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 7-10* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 9/15/05, is acknowledged.

2. Claims 1-4 and 7-10 are pending.

3. Claims 1-3 and 7-9 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1 and 10 are under consideration in the instant application as they read on a pharmaceutical composition comprising an endothelin blocker and an αvβ3 integrin receptor antagonist and a trade package.

5. In view of the amendment filed on 9/15/05, only the following rejections are remained.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 4 and 10 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition or a trade package, comprising as pharmaceutical agent, ET_A endothelin blocker and an αvβ3 integrin receptor antagonist together with an instruction for use of the pharmaceutical agent for the treatment of restenosis after vessel injury or a cardiovascular disorder that involve ET_A receptor and αvβ3 integrin antagonist, does not reasonably provide enablement A pharmaceutical composition for the treatment or prevention of cardiovascular diseases comprising an endothelin blocker and an avb3 integrin receptor antagonist in claim 4 or a trade package thereof in claim 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 2/28/05.

Applicant's arguments, filed 9/15/05, have been fully considered, but have not been found convincing.

Applicant disagree with the Examiner's conclusion that the use of ET_B antagonists as a therapeutic agent is unpredictable. Applicant points in addition to stating that selective ET_B receptor blockade has never seriously been considered as a therapeutic option, Munter et al also states that the ET receptor subtypes cannot be considered as isolated entities- a cross-talk between ET_A and ET_B receptors with consequences not totally understood (emphasis added by Applicant) so far has been described. Furthermore, Applicant submits that nearly all preclinical and clinical studies have shown that selective ET_A and non-selective ET_A/ET_B receptor blockers are similarly effective (emphasis added by Applicant) in different cardiovascular disease states. Applicant concludes that the preclinical and clinical results clearly dispute the allegation that

ET_A and ET_B antagonists are mutually exclusive in that they reach opposing endpoints. Moreover, Applicant refers to Munter et al teachings that the vasodilator component of the ET_B receptors is much more pronounced than the constrictive action in normally functioning (emphasis added by Applicant) vascular endothelium. It is, however, not clear what the predominant function of ET_B in injured (emphasis added by Applicant) vascular endothelium as in various cardiovascular disorders, in particular restenosis after PTCA. Applicant concluded that there is not a sufficient and well-founded reason to suspect that ET_B blockade would not result in beneficial outcome.

However, ET_A is located mainly on vascular smooth muscle cells and is responsible for mediating vasoconstriction and proliferation. ET_B is present predominantly on endothelial cells and mediates vasorelaxation as well as ET-1 clearance. Activation of smooth muscle ET_BR causes vasoconstriction. It is unclear which patients would be candidates for treatment with ET_A blocker and which patients would be candidates for treatment with ET_B blocker. There is insufficient guidance and direction in the specification for cardiovascular diseases or conditions that would be targeted with either endothelin blockers. While the non-selective and selective antagonist may both find useful clinical applications, though the relative merits of each in any particular condition is not clear. In addition, changes in receptor subtype distribution under different pathologic conditions and different patient populations will play a crucial role in the treatment or prevention of cardiovascular diseases. Munter et al teaches that a direct head to head comparison with equally effective ET_A versus ET_A/ET_B receptor blockade, which would clarify the issue, has not yet been performed (see section 2.1, last sentence). Therefore, the use of ET_B antagonists as a therapeutic agent for any cardiovascular disease is unpredictable. It appears that Applicant admits that function of ET_B in injured vascular endothelium as in various cardiovascular disorders, in particular restenosis after PTCA is not clear.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 4 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchengast *et al* (provided in the International Report and cited on the PTO-892 as reference Y) in view of Srivatsa *et al* (provided in the International Report and cited on the PTO-892 as reference W) for the same reasons set forth in the previous Office Action mailed 2/28/05.

Applicant's arguments, filed 9/15/05, have been fully considered, but have not been found convincing.

Applicant argues that (1) selection of one particular combination of two approaches from a large number of possibilities without any guidance was not obvious. Applicant contends that as early as 1995 a large number of small molecule approaches to the prevention or rstenosis were well-known in the art. The approaches listed in reference U (Morris et al) were by no means exhaustive as the use of αvβ3 integrin receptor inhibitors for reducing restenosis was not mentioned even though supporting experimental evidence had been published earlier (references 19, 22 and 23 of Srivatsa). Applicant concludes that it can be said that a very large number of small molecule approaches to the prevention of restenosis were known at the priority date of the present application, the number of possible combinations of these known approaches would be even higher.

However, Morris et al as well as references 19, 22 and 23 of Srivatsa et al is not part of the 103(a) rejection, therefore, is considered irrelevant to the rejection. With regard to the subject matter of the present arguments, the use of combinations therapy is so notoriously well known as to be capable of being taken by official notice. When the ingredients are associated in an obvious manner set forth in the claims, they do not co-act with each other in any new or unexpected way and define nothing patentable over the prior art. Kirchengast *et al* teach 8 endothelin blockers such as BQ 123, SB209670, BMS 182874, TAK 044, FR 139317, LU 135252, Bosentan, A 1277225 and LU135252 that were tested in different models of restenosis (a cardiovascular disorder) in rats and pigs. Kirchengast *et al* also teach that both the selective ET_A receptor antagonist FR 139317 and the mixed $ET_{A/B}$ receptor antagonist TAK 044 were able to reduce neointima proliferation by 76% and 80%, respectively. Further, the balanced $ET_{A/B}$ receptor antagonist SB 209670 was shown to reduce the neointima/media ration by 52%. Furthermore, BMS 182874 and LU135252 were able to reduce neointima/media ration by 35% and 25%, respectively (see page 552 under Endothelin antagonism in experimental restenosis and table 1 in particular). Srivatsa *et al* teach that selective αvβ3 integrin blockade potently limits neointimal hyperplasia and lumen stenosis following deep coronary arterial stent injury (a cardiovascular disorder). Srivatsa *et al* also tested the effect of the XJ 735, a cyclic Arg-Gly-Asp (RGD) peptidomimetic αvβ3 antagonist on neointimal hyperplasia and lumen stenosis in a porcine coronary injury model (see age 424, 2nd col., at the end of the 2nd paragraph in particular). Srivatsa *et al* concluded that in large animal coronary stent restenosis model, use of a selective high affinity αvβ3 antagonist resulted in a marked reduction in neointimal hyperplasia and lumen stenosis (see page 426, last paragraph in particular). It is obvious to employ these components in combination for their known functions and to optimize the amount of each additive. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the endothelin blockers taught by Kirchegast *et al*, with the selective αvβ3 integrin antagonist XJ 735 taught by Srivatsa *et al*.

Further, regarding the large number of possibilities without any guidance, the Examiner notes that Applicant's claims are directed to a large number of possibilities without any guidance to the

particular combination too. However, the combined reference teachings provide specific compounds in experimental restenosis that would have been obvious to combined because their combined use is clearly be expected to be more efficient than the use of each compound individually.

Applicant argues that since the precise molecular processes responsible for pathological restenosis were not well understood at the time (Kirchengast et al), and there were mixed results for various small molecule approaches (Morris et al), it would not have been obvious to a person skilled in the art which particular approach or what exact combination of approaches to pursue. Moreover, none of the prior art document, N-Q and U-W, provided any indication that the particular combination of an ET blocker with an αvβ3 integrin receptor antagonist may be used for the treatment of restenosis.

Again, neither Morris et al nor documents N-Q are part of the rejection, and considered irrelevant. With regard to the subject matter of the present arguments, however, those references have done nothing different then Applicant's specification with respect to the particular approach or what exact combination of approaches to pursue. The specification does not appear to add anything not taught by the prior art. If the specification is enabling, so is the prior art reference.

Applicant argues that even though, theoretically, a person skilled in the art could combine two compositions each of which is taught by the prior art to be useful for the same purpose, in reality, there is no reason to believe that the person skilled in the art would have chosen the particular combination of an ET blocker and an αvβ3 integrin receptor antagonist from the extremely large number of possibilities.

Contrary to applicant's assertion, Kirchengast *et al* and Srivatsa et al provides specific number ET blockers (8 endothelin blockers) and αvβ3 integrin receptor antagonists such as XJ 735, a cyclic Arg-Gly-Asp peptidomimetic to be combined in a method for treating restenosis. When the ingredients are associated in an obvious manner set forth in the claims, they do not co-act with each other in any new or unexpected way and define nothing patentable over the prior art.

Applicant argues that (2) the lack of similar disclosure indicates the non-obviousness of the present combination. Applicant argues that the potential use of an ET blocker for treating cardiovascular diseases was known as early as 1994 if not earlier. The potential use of an avb3 integrin antagonist for treating restenosis was also known as early as 1994. Applicant contends that five years lapsed between 1994 and the priority date of the present application without any disclosure of the use of an ET blocker in combination with an avb3 integrin receptor antagonist for the treatment of restenosis. Applicant argues that given the fact that cardiovascular disease is the number one disease of developed countries and that about a quarter of a million patients per year suffered from restenosis following PTCA in the 1990s, it can be said that there was agreat need for effective treatments of restenosis. Furthermore, given the fact that the cardiovascular field is one of the most researched fields in modern biomedical sciences, the absence of any disclosure similar to the present application in the five-year period can only be interpreted to

mean that the combination of the present application was not obvious to a person skilled in the art.

However, "The mere age of the references is not persuasive of the unobviousness of the combination of their teachings, absent evidence that, notwithstanding knowledge of the references, the art tried and failed to solve the problem." In re Wright, 569 F.2d 1124, 1127, 193 USPQ 332, 335 (CCPA 1977) (100 year old patent was properly relied upon in a rejection based on a combination of references.). See also Ex parte Meyer, 6 USPQ2d 1966 (Bd. Pat. App. & Inter. 1988) (length of time between the issuance of prior art patents relied upon (1920 and 1976) was not persuasive of unobviousness). See MEPE 2145.

10. Claim 10 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchengast *et al* (provided in the International Report and cited on the PTO-892 as reference Y) in view of Srivatsa *et al* (provided in the International Report and cited on the PTO-892 as reference W) as applied to claims 4-6 above, and further in view of US Pat. No. 4,761,406 for the same reasons set forth in the previous Office Action mailed 2/28/05.

Applicant's arguments, filed 9/15/05, have been fully considered, but have not been found convincing.

Applicant disagree with the Examiner for the reasons detailed above. Applicant further asserts that combination of an ET blocker and an avb3 integrin receptor antagonist is patentable as discussed above. Applicant concludes that a trade package comprising said combination of agents is patentable.

However, based on the totality of the record as detailed above, the evidence of obviousness found in the combined reference teachings with Applicant's argument for nonobviousness. The Examiner concludes that the claimed invention encompassed by instant claims 4 and 10 would have been obvious as a matter of law under 35 U.S.C 103(a).

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
January 6, 2006

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